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FOCUS SEMINAR: OXIDATIVE STRESS AND CARDIOVASCULAR DISEASE

STATE-OF-THE-ART REVIEW

Impact of Oxidative Stress on the Heart and Vasculature

Part 2 of a 3-Part Series

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ABSTRACT

Vascular disease and heart failure impart an enormous burden in terms of global morbidity and mortality. Although there are many different causes of cardiac and vascular disease, most causes share an important pathological mechanism: oxidative stress. In the failing heart, oxidative stress occurs in the myocardium and correlates with left ventricular dysfunction. Reactive oxygen species (ROS) negatively affect myocardial calcium handling, cause arrhythmia, and contribute to cardiac remodeling by inducing hypertrophic signaling, apoptosis, and necrosis. Similarly, oxidative balance in the vasculature is tightly regulated by a wealth of pro- and antioxidant systems that orchestrate region-specific ROS production and removal. Reactive oxygen species also regulate multiple vascular cell functions, including endothelial and smooth muscle cell growth, proliferation, and migration; angiogenesis; apoptosis; vascular tone; host defenses; and genomic stability. However, excessive levels of ROS promote vascular disease through direct and irreversible oxidative damage to macromolecules, as well as disruption of redox-dependent vascular wall signaling processes. (J Am Coll Cardiol 2017;70:212–29) © 2017 by the American College of Cardiology Foundation.

With the basic biology of oxidative stress and telomeres already reviewed in Part 1 of this series, here in Part 2 we turn our attention to the impact of oxidative stress on the heart and vasculature, and, in particular, to the pathophysiological role of oxidative stress in heart failure and vascular disease (Central Illustration).

PATHOPHYSIOLOGICAL ROLE OF OXIDATIVE STRESS IN HEART FAILURE

Heart failure (HF) is characterized by activation of the sympathetic nervous and renin-angiotensin-aldosterone systems. This neuroendocrine activation is associated with oxidative stress in the myocardium

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and vasculature. As outlined in Part 1 of this review, oxidative stress is an imbalance between the generation and detoxification of reactive oxygen species (ROS) (1,2). In patients with HF, oxidative stress occurs in the myocardium (3,4) and plasma, and correlates with left ventricular (LV) dysfunction (5). Reactive oxygen species negatively affect disposition of myocardial calcium (Ca^{2+}), cause arrhythmia, and contribute to cardiac remodeling by inducing hypertrophic signaling, apoptosis, and necrosis (6,7). Enzymatic sources for ROS, such as the nicotinamide adenine dinucleotide phosphate (NADPH) oxidases (NOXs), uncoupled nitric oxide (NO) synthase, and mitochondria are all considered relevant sources of ROS in HF, causing vascular and myocardial dysfunction (2). Importantly, mitochondria amplify ROS derived from NOXs and may thereby function as "redox hubs" in cardiac physiology and disease (8,9).

In the initial part of this review, we focus on the crucial role of ROS in HF that causes vascular and myocardial dysfunction. We also address the vitamin paradox by exploring why attempts to reduce oxidative stress in patients at cardiovascular risk (e.g., with vitamin E) caused, rather than prevented, the development of HF (2).

ENZYMATIC SUPEROXIDE SOURCES IN HF AND FUNCTIONAL CONSEQUENCES FOR THE VASCULATURE AND MYOCARDIUM. NADPH oxidase. In experimental models and patients with HF, myocardial superoxide (O_2^-)-generating NOX activity is increased (3,4). Specific NOX isoforms exist in endothelial cells (ECs), smooth muscle cells (SMCs), adventitial cells, and cardiac myocytes (10). In the latter isoform, physiological stretch activates the sarcolemmal and transverse tubule-localized NOX2 (X-ROS signaling), and these ROS sensitize nearby ryanodine receptors to trigger Ca^{2+} release from the sarcoplasmic reticulum (11). This mechano-chemotransduction also involves NO synthases and calmodulin-dependent protein kinase II (12), raising the possibility that peroxynitrite ($ONOO^-$) and methionine oxidation are involved.

Canonical activation of NOX2 occurs through G_q-coupled angiotensin II (Ang II) receptors. Subpressor doses of Ang II induce cardiac hypertrophy that is abolished by NOX2 deletion, although NOX2 deletion does not prevent HF development in response to severe pressure overload induced by aortic constriction (6). In animal models of myocardial infarction, NOX2 inactivation reduces infarct size and ameliorates HF development, but it is unclear whether this is related to vascular NOX or phagocytic NOX located in inflammatory cells. At higher Ang II doses that induce hypertension, depletion of inflammatory cells attenuates some features of oxidative stress, such as endothelial dysfunction, vascular ROS formation, and also arterial hypertension (13).

In contrast to NOX2, NOX4 does not require any regulatory subunits, and it constitutively produces hydrogen peroxide (H_2O_2), rather than O_2^- (6). In the heart, NOX4 is located in the endoplasmic reticulum (ER), the nucleus, and possibly also in mitochondria (6). Stimuli that activate NOX4 include ischemia, hypoxia, and adrenergic stimuli, which are all present and enhanced in HF. However, the role of NOX4 in HF development is controversial, as mice lacking cardiac NOX4 have been shown to exhibit both reduced and aggravated maladaptive remodeling in pressure overload-induced HF, using differing model systems (6,14). Furthermore, NOX4-deficient mice exhibit partial protection against ischemic myocardial injury (15), whereas double-knockout of NOX2 and NOX4 increases susceptibility to ischemic myocardial injury, perhaps through altered ROS production and downregulation of stress-response pathways such as hypoxia-inducible factor (HIF)-1α (15). As both myocardial and endothelial NOX4 promote angiogenesis, their absence from cardiac myocytes or vessels could also lead to capillary rarefaction and sensitivity to ischemic injury (16,17).

Mitochondria. In mitochondria, O_2^- is generated by the electron transfer chain (ETC) but is rapidly dismutated to H_2O_2 by manganese-dependent superoxide dismutase (Mn-SOD). H_2O_2 is then eliminated by antioxidative enzymes (i.e., glutathione peroxidase and peroxiredoxin), which require NADPH for regeneration (**Figure 1**). In HF, a functional blockage of complex I provokes excessive production of O_2^-, which is transformed to H_2O_2 and hydroxyl radicals ($OH^•$) (through the Fenton reaction) (18). In addition to increased production, the elimination of ROS in the mitochondrial matrix is compromised by dynamic oxidation of the antioxidative capacity, resulting in increased net emission of ROS from mitochondria (**Figure 1**) (this is the concept of "redox-optimized ROS balance" [19,20]).

In mitochondria, the Krebs cycle generates nicotinamide adenine dinucleotide (NADH), which donates electrons to the ETC to produce ATP. However, the Krebs cycle also produces substrates that regenerate NADPH, which, in turn, regenerates antioxidative enzymes (**Figure 1**) (20,21). In HF, defects in cytosolic Ca^{2+} and Na^+ disposition in cardiac myocytes (e.g., reduced release of sarcoplasmic reticulum Ca^{2+} and elevated Na^+) reduce accumulation of

ABBREVIATIONS AND ACRONYMS

Ang II = angiotensin II

eNOS = endothelial nitric oxide synthase

H_2O_2 = hydrogen peroxide

HF = heart failure

NADPH = nicotinamide adenine dinucleotide phosphate

NO = nitric oxide

NOX = nicotinamide adenine dinucleotide phosphate oxidase (NADPH oxidase)

O_2^- = superoxide

ROS = reactive oxygen species

SOD = superoxide dismutase